## Editorial Comment

# Is Obesity Due to a Heritable Difference in 'Set Point' for Adiposity?

RUDOLPH L. LEIBEL, MD, *New York*

Adipose tissue lipid content reflects the long-term balance between energy intake and output. Small positive imbalances in this relationship over long periods of time can result in the accumulation of large amounts of excess fat. An adult human ingests about 214,000 kilojoules (900,000 kilocalories) per year. The caloric content of adipose tissue is about 1.7 kJ (7 kcal) per gram. Thus, a cumulative "error" in the balance of energy intake and output of as little as 5% could result in accumulations (or losses) of 6 kg of adipose tissue per year. Body weight or composition in "free-feeding" humans generally does not show yearly fluctuations of this magnitude. In fact, body weight remains remarkably stable over long periods of time, even in the absence of conscious efforts to control it, and experimental perturbations of body weight are met by resistive metabolic forces tending to return body composition to its starting state.[1,2] Observations of this sort have been taken as evidence for the existence of a "set point" for body fatness, though alternative possibilities[3] have been suggested.

Is there a set point for fatness in humans or animals? If so, what is regulated (fat cell size, number, total fat mass), what is sensed (a metabolite of fat, a peptide secreted by fat), and where is the sensor (brain, liver)? Although many provocative experiments have been done that probed these possibilities, the answers to these questions are not known.

A number of animal models support the idea of a set point for adiposity. Specific regions within the brain regulate food intake and play a role in metabolic efficiency.[4] The latter influence may be mediated by autonomic efferents.[5] Although it is clear that anatomically diverse regions of the central nervous system participate in feeding behavior, the function of the ventromedial and lateral aspects of the hypothalamus provides a good paradigm for the existence of such sites within the brain.[6] Ablative lesions of the ventromedial and lateral aspects of the hypothalamus result in respective increases and decreases in body fat that reflect coordinate changes in both food intake and energy expenditure.[7] The fact that such lesions cause alterations in both food intake and energy efficiency has suggested that these regions of the brain may subserve a set-point function, rather than controlling a single efferent or afferent limb (such as food intake or energy efficiency) of the regulatory process. Animals with lesions in these parts of the central nervous system generally regulate their weights normally about the new set points created by ablative procedures. This phenomenon again supports the notion of a central regulator of adiposity per se.[7]

Genetically obese rodents include autosomal dominant (Yellow and Adipose mice), recessive mutations (obese, diabetic, fat, and tubby mice; fatty rats), and "polygene" obese mice such as the New Zealand Obese.[8] The existence of these mutations indicates that in a mammalian system, obesity or diabetes mellitus, or both, may result from a single gene mutation. Human syndromes such as the Prader-Willi and Bardet-Biedl syndromes indicate, likewise, that a purely genetic basis may exist for some (very rare) forms of human obesity.[9-11]

The rodent mutations are particularly intriguing because they represent potential access to single genes regulating energy homeostasis that generate phenotypes (hyperphagia and increased energy efficiency) closely resembling those seen in obese humans. Similar phenotypes are produced by mutations occurring on four different chromosomes in mice, suggesting that these genetic loci may all subserve a single regulatory pathway.[12] Evidence in support of this idea comes from parabiosis (shared blood flow) experiments in mice that suggest that the *ob* (chromosome 6) locus codes for a circulating satiety factor for which the *db* (chromosome 4) locus product is the receptor.[13] An additional important phenotypic aspect of these animals is the longer survival of heterozygotes *(ob)* during a total fast,[14] a finding consistent with a putative selective advantage conferred by a "thrifty" genotype.[15]

The severity of the diabetes that develops in these mice is highly dependent on the background strain on which the gene is engrafted. Thus, *ob/ob* on the C57BL/6J background produces obese mice with transient insulin resistance, which is compensated by pancreatic $\beta$-cell hypertrophy. On the C57BL/KsJ background, homozygosity for *ob* results in severe diabetes with ultimate pancreatic failure ($\beta$-cell atrophy) and shortening of the lifespan.[16] A wide variation in phenotype for a single mutant allele, due to modulating effects of the background genome, suggests that a few allelic variants of these genes, segregating in the human population, might be sufficient to account for the heritability of obesity and diabetes.

Efforts to quantify the heritability of obesity in humans are confounded by problems that derive from the (apparent) polygene contributions to phenotype, the powerful effects of environmental circumstance on the penetrance of whatever gene(s) may be involved, and the experimental use of phenotypes (such as weight or weight-for-height constructs) that do not make the fine distinctions (such as body composition, energy efficiency, hedonic factors in food intake) necessary to identify differences that may define subsets of causes. A variety of studies, including those

(Leibel RL: Is obesity due to a heritable difference in 'set point' for adiposity? West J Med 1990 Oct; 153:429-431)

From the Laboratory of Human Behavior and Metabolism, Rockefeller University, New York.
Reprint requests to Rudolph L. Leibel, MD, Laboratory of Human Behavior and Metabolism, Rockefeller University, New York, NY 10021.

of twins and adopted children, find that between 5% and 80% of the variance in adiposity is attributable to genotype.[17-20] A portion of the wide range of values is due to the failure to distinguish total transmissible variances (which includes genotype plus environmental interactions) from pure, additive genetic effects.[19] The genetic influence on body shape (distribution of fat) appears to be as strong as or stronger than that for total body fat.[19] Strong genetic contributions have also been shown for fat deposition during overfeeding and for energy expenditure at low levels of exercise.[21] Experiments in animals suggest that early nutritional experiences may influence the penetrance of obesity-producing genes (such as in Zucker rats) in older animals,[22] and studies in humans suggest qualitatively similar effects of the prenatal environment.[23,24] In the aggregate, however, studies of feeding practices and rates of weight gain in infancy have not suggested an important role for either of these factors in the risk of obesity in childhood or adolescence.[25]

In the case of the control of body composition, it is clear that the phenotype is a changeable reflection of complex interactions of genotype and environment. Industrialized cultures, with their ready access to calorically dense foods and the diminished need for physical exertion, are optimal environments for the maximum expression of genetic predispositions to the maintenance of high levels of body fatness.

In this issue of the journal, Weigle takes positions that are implicitly influenced by some of the physiologic and genetic considerations described above.[26] Several specific points concerning his arguments may be made:

- What is the proper approach to the management of moderate degrees of obesity? As indicated by Weigle's discussion, there is considerable debate about the health risks of mild to moderate adiposity—that is, 110% to 130% above "desirable" body weight. The U- or J-shape of the relationship between body weight (or body mass index [BMI]) and all-cause mortality demonstrated by various epidemiologic studies is largely an artifact of the failure to control for one or more of the following variables: cigarette smoking; inappropriate factoring out of the biologic effects of obesity that confer mortality as intervening variables (hypertension); and a failure to control for weight loss due to subclinical disease.[27] When these are considered, it appears that "minimum mortality occurs at weights at least 10% lower than US average weights," and that even mild degrees of obesity confer an increased mortality risk.[27] This argument has resurfaced in a paper published since Weigle wrote his review. In a large eight-year prospective study of 115,886 nurses 30 to 55 years of age, even mild degrees of obesity were associated with a 20% to 30% increased coronary artery disease risk; there was no broad plateau in lower portions of the function relating BMI to coronary artery disease risk. Women with the lowest BMIs ($< 21$) had the lowest risk of coronary events, and rates increased for all quintiles with higher BMIs. Thus, there did not appear to be a "safe" level of mild adiposity in this study.[28]
- It has been difficult to show an important adverse metabolic consequence of obesity separate from those conveyed by this condition's effects on blood pressure and carbohydrate and lipid homeostasis. Whether such an influence exists is of biologic interest but probably of little therapeutic significance. The medical consequences of obesity can, in most instances, be treated by weight reduction, medication, or a combination of the two. Given the apparent adverse consequences of even modest degrees of obesity, it seems important to counsel prevention, remembering that childhood obesity is not necessarily a good predictor of obesity in adulthood[29] and that an overaggressive restriction of calories in a child can restrict the growth of lean tissues.[25] In adults, conscientious efforts at weight control should be recommended for virtually all obese persons—perhaps with special attention to those showing evidence of adverse medical consequences of their excess adiposity. The likelihood of success is clearly greatest in those with the least severe obesity. In instances where the maintenance of reduced weight proves impossible, attention should be shifted to pharmacologic treatment of the medical consequences of obesity because they convey the major portion of the risk attributable to obesity.
- Body shape (distribution of fat) conveys a substantial part of the medical risk associated with obesity. Careful studies by Kissebah and collaborators have documented a reduction in hepatic insulin extraction in persons with upper-body obesity leading to peripheral hyperinsulinemia and diminished peripheral insulin sensitivity.[30] This group has also shown evidence of a role for circulating androgens in the preferential deposition of intra-abdominal fat.[31] Body shape changes little following weight reduction in adults, so that "apples" and "pears" tend to become reduced versions of the same fruit.[32,33] Despite this, weight reduction leads to improvement in these medical risk factors, suggesting that absolute abdominal adiposity is more important than is relative (waist:hip ratio) adiposity in this regard. For that reason, normative data should be developed relating the abdominal circumference to a power function of stature—comparable to the body mass index (weight: height$^2$)—rather than relying on the waist:hip ratio, which does not give as direct a measure of absolute abdominal adiposity.
- The enhanced energy efficiency of formerly obese persons apparently contributes to the high recidivism rate to obesity.[34,35] It is not yet clear to which metabolic compartment(s) this enhanced efficiency may be attributed. It appears, however, that physical activity (total motion, mechanical efficiency, or both), rather than resting metabolic rate or the thermic effect of feeding, is the most likely candidate.[36] Whether these differences precede—and may therefore be causal of—obesity is not known. Studies in both infants[37] and adults[38] suggest that low energy output precedes the onset of obesity. The existence of such enhanced energy efficiency cannot, however, be the complete answer. Still unexplained is why energy intake does not simply decrease to match the lower energy output, thus preventing the imbalance of intake versus output that leads to obesity. This discordance of food intake and energy output highlights the critical interaction of behavior and metabolism in the pathophysiology of obesity and indicates the conceptual error inherent in efforts to define obesity as exclusively a disorder of either behavior or metabolism.[39]

The set point does not seem to encode a specific level of food intake or energy output but rather an amount or proportion of fatness. Thus, obese and never-obese persons regulate normally about their "usual" body compositions, making adjustments in food intake and energy expenditure that are appropriate to the maintenance of that degree of weight. Intake and output become matched once a specified level of fat storage is achieved.[38] An understanding of the biomolecular basis for this regulatory process may ultimately enable its developmental or pharmacologic manipulation. Meanwhile, conscientious, lifelong attention to diet and levels of physical activity must be employed to defeat

the biologic drive to high levels of adiposity and to enhance the quality and length of life in those to whom nature may have dealt a high "set point."

**REFERENCES**


1. Sims EAH, Danforth E, Horton ES, et al: Endocrine and metabolic effects of experimental obesity in man. Recent Prog Horm Res 1973; 29:457-496

2. Apfelbaum M, Bostsarron J, Lacatis D: Effect of caloric restriction and excessive caloric intake on energy expenditure. Am J Clin Nutr 1971; 24:1405-1409

3. Sukhatme PV, Margen S: Autoregulatory homeostatic nature of energy balance. Am J Clin Nutr 1982; 35:355-365

4. Luiten PGM, Horst GJT, Steffens AB: The hypothalamus, intrinsic connections and outflow pathways to the endocrine system in relation to the control of feeding and metabolism. Prog Neurobiol 1987; 28:1-54

5. Bray GA: Genetic and hypothalamic mechanisms for obesity—Finding the needle in the haystack. Am J Clin Nutr 1989; 50:891-902

6. Morley JE: Neuropeptide regulation of appetite and weight. Endocr Rev 1987; 8:256-287

7. Keesey RE: A set-point analysis of the regulation of body weight, *In* Stunkard AJ (Ed): Obesity. Philadelphia, WB Saunders, 1980, pp 144-165

8. Festing MFW (Ed): Animal Models of Obesity. New York, Oxford University Press, 1979

9. Bray GA, Dahms WT, Swerdloff RS, et al: The Prader-Willi syndrome: A study of 40 patients and a review of the literature. Medicine (Baltimore) 1983; 62:59-80

10. Donlon TA: Similar molecular deletions on chromosome 15q11.2 are encountered in both the Prader-Willi and Angelman syndromes. Hum Genet 1988; 80:322-328

11. Bray GA: Classification and evaluation of the obesities. Med Clin North Am 1989; 73:161-184

12. Leibel RL, Bahary N, Friedman JM: Genetic variation and nutrition in obesity: Approaches to the molecular genetics of obesity, *In* Simopoulos AP, Childs B (Eds): Genetic Variation and Nutrition. Basel, Karger, 1990

13. Coleman DL: Obese and diabetes: Two mutant genes causing diabetes-obesity syndromes in mice. Diabetologia 1978; 14:141-148

14. Coleman DL: Acetone metabolism in mice: Increased activity in mice heterozygous for obesity genes. Proc Natl Acad Sci USA 1980; 77:290-293

15. Neel JV: Diabetes mellitus: A 'thrifty' genotype rendered detrimental by 'progress'? Am J Human Genet 1962; 14:353-362

16. Leiter EH: The genetics of diabetes susceptibility in mice. FASEB J 1989; 3:2231-2241

17. Stunkard AJ, Foch TT, Hrubec Z: A twin study of human obesity. JAMA 1986; 256:51-54

18. Stunkard AJ, Sorensen TI, Hanis C, et al: An adoption study of human obesity. N Engl J Med 1986; 314:193-198

19. Bouchard C: Genetic factors in obesity. Med Clin North Am 1989; 73:67-81

20. Borjeson M: The etiology of obesity in children. Acta Pediatr Scand 1976; 65:279-287

21. Bouchard C, Tremblay A, Nadeau A, et al: Genetic effect in resting and exercise metabolic rates. Metabolism 1989; 38:364-370

22. Johnson PR, Stern JS, Greenwood MRC, et al: Effect of early nutrition on adipose cellularity and pancreatic insulin release in the Zucker rat. J Nutr 1973; 103:738-743

23. Ravelli GP, Stein Z, Susser MW: Obesity in young men after famine exposure in utero and early infancy. N Engl J Med 1976; 295:349-353

24. Pettitt DJ, Baird HR, Aleck KA, et al: Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy. N Engl J Med 1983; 308:242-245

25. Rosenbaum M, Leibel RL: Pathophysiology of childhood obesity. Adv Pediatr 1988; 35:73-137

26. Weigle DS: Human obesity—Exploding the myths. West J Med 1990 Oct; 153:421-428

27. Manson JE, Stampfer MJ, Hennekens CH, et al: Body weight and longevity. JAMA 1987; 257:353-358

28. Manson JE, Colditz GA, Stampfer MJ, et al: A prospective study of obesity and risk of coronary heart disease in women. N Engl J Med 1990; 322:882-889

29. Braddon FEM, Rodgers R, Wadsworth MEJ, et al: Onset of obesity in a 36-year birth cohort study. Br Med J 1986; 293:299-303

30. Peiris AN, Mueller RA, Smith GA, et al: Splanchnic insulin metabolism in obesity: Influence of body fat distribution. J Clin Invest 1986; 78:1648-1657

31. Peiris AN, Mueller RA, Struve MF, et al: Relationships of androgenic activity to splanchnic insulin metabolism and peripheral glucose utilization in premenopausal women. J Clin Endocr Metab 1987; 64:162-169

32. Leibel RL, Edens NK, Fried SK: Physiologic basis for the control of body fat distribution in humans. Annu Rev Nutr 1989; 9:417-443

33. Presta E, Leibel RL, Hirsch J: Regional changes in adrenergic receptor status during hypocaloric intake do not predict changes in adipocyte size or body shape. Metabolism 1990; 39:307-315

34. Leibel RL, Hirsch J: Diminished energy requirements in reduced-obese patients. Metabolism 1984; 33:164-170

35. Geissler CA, Miller DS, Shah M: The daily metabolic rate of the post-obese and the lean. Am J Clin Nutr 1987; 45:914-920

36. Weigle DS, Sande KJ, Iverius PH: Weight loss leads to a marked decrease in nonresting energy expenditure in ambulatory human subjects. Metabolism 1988; 37:930-936

37. Roberts SB, Savage J, Coward WA, et al: Energy expenditure and intake in infants born to lean and overweight mothers. N Engl J Med 1988; 318:461-466

38. Ravussin E, Lillioja S, Knowler WC, et al: Reduced rate of energy expenditure as a risk factor for body-weight gain. N Engl J Med 1988; 318:467-472

39. Hirsch J: Obesity: A perspective, *In* Bray GA (Ed): Recent Advances in Obesity Research: II. London, Newman Publishing Ltd, 1978, pp 1-5